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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/374,721	08/13/1999	JOHN HENRY KENTEN	IGN-2004	4071

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EXAMINER	
ZEMAN, ROBERT A	
ART UNIT	PAPER NUMBER
1645	30

DATE MAILED: 08/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/374,721	Applicant(s) KENTEN ET AL.	
	Examiner Robert A. Zeman	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-87 and 91-116* is/are pending in the application.

4a) Of the above claim(s) *1-81 and 101-116* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *82-87 and 91-100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment and response filed on 6-13-2003 are acknowledged. Claims 91 and 93-94 have been amended. Claims 1-87 and 91-116 are pending. Claims 1-81 and 101-116 remain withdrawn from consideration. Claims 82-87 and 91-100 are currently under examination.

This application contains claims 1-81 and 101-116 drawn to an invention nonelected with traverse in Paper No. 13. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections Withdrawn

The rejection of claims 91-94 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by being dependent on a canceled claim is withdrawn in light of the amendment thereto.

Claim Rejections Maintained

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejections of claims 82-87 and 91-100 under 35 U.S.C. 103(a) as being unpatentable over Mouritsen et al. (WO 95/05849) in view of van der Zee et al. (Vaccine Vol. 13, No. 8, pages 753-758, 1995) is maintained for of record.

Applicant argues:

1. Mouritsen et al. teach the use of ubiquitin in a fusion protein as a self-epitope whereas Applicant teaches the use of ubiquitin in a fusion protein as a T-cell epitope.

2. Mouritsen et al. do not teach the ability of ubiquitin to generate an immune response as a T-cell epitope in a fusion protein.

3. While Mouritsen et al. teach that the disclosed ubiquitin fusion proteins containing T cell epitopes HEL (50-61) and OVA (325-336) generate an immune response directed not only to the T-cell epitopes but the ubiquitin self-epitope, one of skill in the art could not say to any degree of certainty that said immune response was due to ubiquitin.

4. van der Zee et al. do not teach the use of ubiquitin for generating an immune response to GnRH.

5. The ability of ubiquitin to generate an immune response to a self-epitope in a fusion protein was an **unexpected result**.

Applicant's arguments have been fully considered and deemed unpersuasive.

The instant invention is drawn to methods for stimulating an immune response in an animal, the immune response being directed to a self-epitope utilizing a ubiquitin fusion protein comprising ubiquitin fused to one or more epitope containing segments comprising tow or more identical or non-identical non-ubiquitin self epitopes (either GnRH or growth hormone).

In response to applicant's argument that the references fail to show certain features of applicant's invention (Points 1 and 2), it is noted that the features upon which applicant relies (i.e., ubiquitin is a T-cell epitope) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

With regard to Point 3, as pointed out by Applicant Mouritsen et al. disclose that their fusion proteins induce an immune response to the "self antigen" as required by the rejected claims.

In response to applicant's arguments against the references individually (i.e. Point 3), one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

With regard to Applicant's assertion of unexpected results (Point 5), Applicant has failed to provide evidence supporting said assertion. The MPEP states:

716.02(b) Burden on Applicant
BURDEN ON APPLICANT TO ESTABLISH RESULTS ARE UNEXPECTED AND SIGNIFICANT
The evidence relied up should establish "that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance." *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992) (Mere conclusions in appellants' brief that the claimed polymer had an unexpectedly increased impact strength "are not entitled to the weight of conclusions accompanying the evidence, either in the specification or in a declaration."); *Ex parte C*, 27 USPQ2d 1492 (Bd. Pat. App. & Inter. 1992) (Applicant alleged unexpected results with regard to the claimed soybean

plant, however there was no basis for judging the practical significance of data with regard to maturity date, flowering date, flower color, or height of the plant.). See also *In re Nolan*, 553 F.2d 1261, 1267, 193 USPQ 641, 645 (CCPA 1977) and *In re Eli Lilly*, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) as discussed in MPEP § 716.02(c).

APPLICANTS HAVE BURDEN OF EXPLAINING PROFFERED DATA

"[A]ppellants have the burden of explaining the data in any declaration they proffer as evidence of non-obviousness." *Ex parte Ishizaka*, 24 USPQ2d 1621, 1624 (Bd. Pat. App. & Inter. 1992).

DIRECT AND INDIRECT COMPARATIVE TESTS ARE PROBATIVE OF NONOBVIOUSNESS

Evidence of unexpected properties may be in the form of a direct or indirect comparison of the claimed invention with the closest prior art which is commensurate in scope with the claims. See *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) and MPEP § 716.02(d) - § 716.02(e). See *In re Blondel*, 499 F.2d 1311, 1317, 182 USPQ 294, 298 (CCPA 1974) and *In re Fouche*, 439 F.2d 1237, 1241-42, 169 USPQ 429, 433 (CCPA 1971) for examples of cases where indirect comparative testing was found sufficient to rebut a *prima facie* case of obviousness.

The patentability of an intermediate may be established by unexpected properties of an end product "when one of ordinary skill in the art would reasonably ascribe to a claimed intermediate the contributing cause' for such an unexpectedly superior activity or property." *In re Magerlein*, 602 F.2d 366, 373, 202 USPQ 473, 479 (CCPA 1979). "In order to establish that the claimed intermediate is a contributing cause' of the unexpectedly superior activity or property of an end product, an applicant must identify the cause of the unexpectedly superior activity or property (compared to the prior art) in the end product and establish a nexus for that cause between the intermediate and the end product." *Id.* at 479.

Additonally,

716.01(c) Probative Value of Objective Evidence

TO BE OF PROBATIVE VALUE, ANY OBJECTIVE EVIDENCE SHOULD BE SUPPORTED BY ACTUAL PROOF

Objective evidence which must be factually supported by an appropriate affidavit or declaration to be of probative value includes evidence of unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. See, for example, *In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984) ("It is well settled that unexpected results must be established by factual evidence." "[A]ppellants have not presented any experimental data showing that prior heat-shrinkable articles split. Due to the absence of tests comparing appellant's heat shrinkable articles with those of the closest prior art, we conclude that appellant's assertions of unexpected results constitute mere argument."). See also *In re Lindner*, 457 F.2d 506, 508, 173 USPQ 356, 358 (CCPA 1972); *Ex parte*

George, 21 USPQ2d 1058 (Bd. Pat. App. & Inter. 1991).

ATTORNEY ARGUMENTS CANNOT TAKE THE PLACE OF EVIDENCE
The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant.

Consequently, in the absence of supporting evidence, Applicant's assertion that the ability of ubiquitin to generate an immune response to a self-epitope in a fusion protein constitutes an unexpected result is deemed unpersuasive.

As outlined previously, Mouritsen et al. disclose the attachment of one or more T cell epitopes into the highly conserved self-protein ubiquitin (see pages 6-7). Mouritsen discloses 2 different ubiquitin fusion proteins: one containing the T-cell epitope ovalbumin (OVA 325-336) and the other containing the T-cell epitope HEL (50-61). Injection of said fusion proteins into mice elicited a strong antibody response to the fusion protein. Moreover, Mouritsen et al. disclose, "the insertion of one **or more** foreign T cell epitopes induces a profound auto-antibody response against said proteins" (see page 6, lines 31-33). Finally, Mouritsen discloses, "the antibody response induced was not necessarily restricted to the inserted T cell epitopes" (see page 6, lines 33-35). van der Zee et al. teach a fusion protein comprising GnRH fused to fimbrae for the development of a contraceptive vaccine for use in domestic animals (see abstract and Figure 4 on page 757). van der Zee et al. also disclose that GnRH is one of the most attractive vaccine components for the immunoneutralization because it is regarded as the key regulatory peptide in the reproduction cycle of mammals (see page

753, column 1). Finally, van der Zee et al. disclose that vaccination of female rats and bull calves with said fusion protein induced not only serological, but also pharmacological effects (see page 757) and as a consequence, that GnRH is a promising candidate for the use in the development of a contraceptive vaccine. Therefore, contrary to Applicant's assertion, would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify ubiquitin fusion proteins disclosed by Mouritsen et al. to use GnRH as the self epitope as disclosed by van der Zee et al. since GnRH is considered the pivotal regulatory peptide in mammalian reproduction and there is a demand for an effective, low cost means of controlling fertility in domestic animals. The resulting fusion protein would benefit from the increased stabilization, increased efficiency of translation and increased preservation of biological activity due to proper folding associated with ubiquitin fusion proteins, as well as the increased efficacy of associated with the use of the GnRH self antigen.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (703) 308-7991. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (703) 308-3909. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Robert A. Zeman
August 7, 2003

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